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PATENT APPLICATION  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Benjamin Lee Hughes, et al. )  
  )  
Serial No. : 09/383,789                    )  
  ) Group Art Unit:  
Filed       : August 26, 1999                ) 1653  
  )  
For         : Method of Administering        ) Examiner  
  : Insulintropic Peptides        ) D. Lukton  
Docket No. : X-12013                        )

DECLARATION UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents  
Arlington, VA 22202-0327

Sir:

I, Ronald K. Wolff, of the City of Carmel, County of Hamilton, State of Indiana, hereby state and declare that:

1. I am the co-inventor of the above referenced U.S. Patent Application Serial No. 09/383,789 (hereinafter the '789 Application). I have reviewed the '789 Application and the outstanding Final Rejection (Paper No. 16) for this application.

2. GLP-1 molecules are biologically active polypeptides that have been shown to normalize blood glucose levels in Type II diabetic patients when administered subcutaneously or intravenously. The '789 Application is directed to a method of administering a GLP-1 molecule by pulmonary means.
3. The '789 Application shows that a GLP-1 molecule can be administered to the lungs and that certain antigenic determinants of the peptide appear in the serum. The Examiner states that the immunoassay employed in the '789 Application to ascertain serum concentration, however, "does not establish that the intact peptide appears in the serum." The Examiner questions whether "the GLP-1 molecule exhibits any particular physiological effect at all when administered to the lung."
4. Under my direction, pharmacodynamic data was generated showing that dry powder formulation comprising a GLP-1 molecule administered by inhalation to dogs decreased plasma glucose compared to the sham air exposure without the GLP-1 molecule.
5. The pharmacodynamic data was obtained as follows:
  - A dry powder formulation of Val<sup>8</sup>-GLP-1(7-37)OH was prepared for inhalation (IH) delivery.
  - A solution formulation of Val<sup>8</sup>-GLP-1(7-37)OH was prepared for subcutaneous (SC) delivery.
  - Glucose was infused at a rate of 18 mg/kg/min intravenously into three normal non-diabetic Beagle dogs.
  - The three dogs were each dosed with three different dosing regimens on three different days:
    - a) sham air exposure without the Val<sup>8</sup>-GLP-1(7-

37)OH molecule on the first day; b) IH administration of the dry powder formulation of Val<sup>8</sup>-GLP-1(7-37)OH at a mean inhaled dose of 0.85 mg/kg, which resulted in an estimated deposited lung dose of 0.21 mg/kg on a second day; and c) SC administration of the solution formulation of Val<sup>8</sup>-GLP-1(7-37)OH at a dose of 0.2 mg/kg on a third day. Blood samples were taken periodically for the determination of plasma glucose.

- The results of the *in vivo* comparison dog study are shown in Table 1 and graphically in Appendix A.

Table 1. Mean Glucose Concentrations (+ SE) in Beagle Dogs Following Sham Air Exposure, IH Administration of the Dry Powder Formulation of Val<sup>8</sup>-GLP-1(7-37)OH, or SC Administration of the Solution Formulation of Val<sup>8</sup>-GLP-1(7-37)OH

Time (minutes)	Sham (SE)	IH Formulation (SE)	SC Formulation (SE)
-90	96	4	105
-80	149	8	147
-70	170	15	143
-60	169	11	159
-50	170	14	142
-40	145	5	146
-30	146	9	133
-20	162	9	145
-10	157	9	127
0	133	9	137
4	153	13	175
8	176	19	202
10	191	16	196
20	213	25	207
30	232	30	179
40	253	53	165
50	214	40	170
60	206	28	160
70	144	2	180
80	135	2	162
90	133	6	155

6. In view of these data, I conclude:
  - a) The dry powder formulation of Val<sup>8</sup>-GLP-1(7-37)OH delivered by IH resulted in a clear decrease in plasma glucose, compared to the sham air exposure without the GLP-1 molecule.
  - b) This data is consistent and corroborate the immunoassay data and assertions in the '789 Application that GLP-1 molecules administered to the lung and detected in the serum are biologically active and useful as described.
7. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.



Ronald Keith Wolff

01 February 2002  
Date

